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Dissecting the 22q13 region to explore the genetic and phenotypic diversity of patients with Phelan-McDermid syndrome

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ABSTRACT

SHANK3-related Phelan-McDermid syndrome (PMS) is caused by a loss of the distal part of chromosome 22, including *SHANK3,* or by a pathological *SHANK3* variant. There is an important genetic and phenotypic diversity among patients who can present with developmental delay, language impairments, autism, epilepsy, and other symptoms. *SHANK3,* encoding a synaptic scaffolding protein, is deleted in the majority of patients with PMS and is considered a major gene involved in the neurological impairments of the patients. However, differences in deletion size can influence clinical features, and in some rare cases, deletions at the 22q13 locus in individuals with *SHANK3*-unrelated PMS do not encompass *SHANK3.* These individuals with *SHANK3*-unrelated PMS still display a PMS-like phenotype. This suggests the participation of other 22q13 genes in the pathogenesis of PMS. Here, we review the biological function and potential implication in PMS symptoms of 110 genes located in the 22q13 region, focusing on 35 genes with evidence for association with neurodevelopmental disorders, including 13 genes for epilepsy and 11 genes for microcephaly and/or macrocephaly. Our review is restricted to the 22q13 region, but future large-scale studies using whole genome sequencing and deep-phenotyping are warranted to develop predictive models of clinical trajectories and to target specific medical and educational care for each individual with PMS.

1. Introduction

Phelan-McDermid syndrome (PMS) is a severe neurodevelopmental disorder (NDD) defined by chromosomal rearrangements impacting the 22q13 region of the long arm of chromosome 22, resulting in a loss of genetic material. Various mechanisms have been reported, including simple small to large deletions, unbalanced translocations, complex genomic rearrangement of the distal part of the long arm of chromosome 22, and the formation of a ring chromosome (Koza et al., this issue). These events arise mainly *de novo*, but germinal mosaicism, balanced chromosomal rearrangements, or rare cases of inherited deletions from the parents are also observed (Bonaglia et al., 2011, 2020; Denayer et al., 2012; Tabet et al., 2017). In individuals with PMS, the deletion size ranges from less than 100 kb to over 9 Mb. For terminal deletions, the most proximal breakpoint in the long arm of chromosome 22 has been mapped in the 22q13.2 cytogenetic region (Sarasua et al., 2014a).

For most individuals with PMS, deletions include the terminal 22q13 region and cover the entire *SHANK3* gene. Interstitial deletions overlapping exons of *SHANK3* and deleterious point mutations in the coding sequence of *SHANK3* are also observed (Durand et al., 2007; Tabet et al.,

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2017; De Rubeis et al., 2018). These observations suggest that *SHANK3* is the main contributor to the PMS phenotype. However, in some patients with clinical features similar to PMS, interstitial deletions do not affect the protein-coding regions of *SHANK3* (Disciglio et al., 2014; Simenson et al., 2014; Palumbo et al., 2018; Li et al., 2020; Wilson et al., 2008). A new classification system was recently proposed to differentiate patients with *SHANK3*-related PMS and *SHANK3*-unrelated PMS (Phelan et al., 2022).

The core phenotypes of PMS are absent or delayed speech, intellectual disability (ID), neonatal hypotonia, global developmental delay, minor morphological features such as large and fleshy hands, and multiple comorbidities with variable expressivity (Phelan and McDermid 2011; Schön et al., this issue). Autism spectrum disorder (ASD) is a prevalent phenotype of PMS, as observed in up to 70–80% of the patients (Soorya et al., 2013; Xu et al., 2020, Schön et al., this issue, van Balkom et al., this issue). Other impairments include epilepsy, sleep disturbance, gastrointestinal abnormalities, lymphedema, renal malformations, and feeding problems (Phelan and McDermid, 2011; Schön et al., this issue). In addition, sensory functioning is often impacted in individuals with PMS, which leads to visual and hearing impairments, reduced pain perception, heat regulation disorder and proprioceptive and vestibular problems (Walinga et al., this issue). Patients with PMS may also exhibit abnormal head growth with microcephaly and macrocephaly in 16% and 17% of cases, respectively (Schön et al., this issue).

In the last decade, a number of studies aiming to understand better the clinical heterogeneity among individuals with PMS were performed in different countries (Soorya et al., 2013; Sarasua et al., 2014b; Tabet et al., 2017; Samogy-Costa et al., 2019; Xu et al., 2020; Nevado et al., 2022). Such investigations found correlations between the size of the deletion and the presence or severity of the PMS symptoms. This has led to the discovery of specific genomic regions that could be associated with an increased risk of absence of speech, gastroesophageal reflux, ophthalmic features, macrocephaly, or epilepsy, among others (Table 1; Sarasua et al., 2014a; Tabet et al., 2017; Jain et al., 2022). In this article, we review the function of 35 genes throughout the 22q13 region deleted in individuals with PMS to provide a state-of-the-art list of the genetic factors at 22q13 that could influence the clinical trajectories of patients with PMS.

2. Definition of the 22q13 region, PMS deletions and gene lists

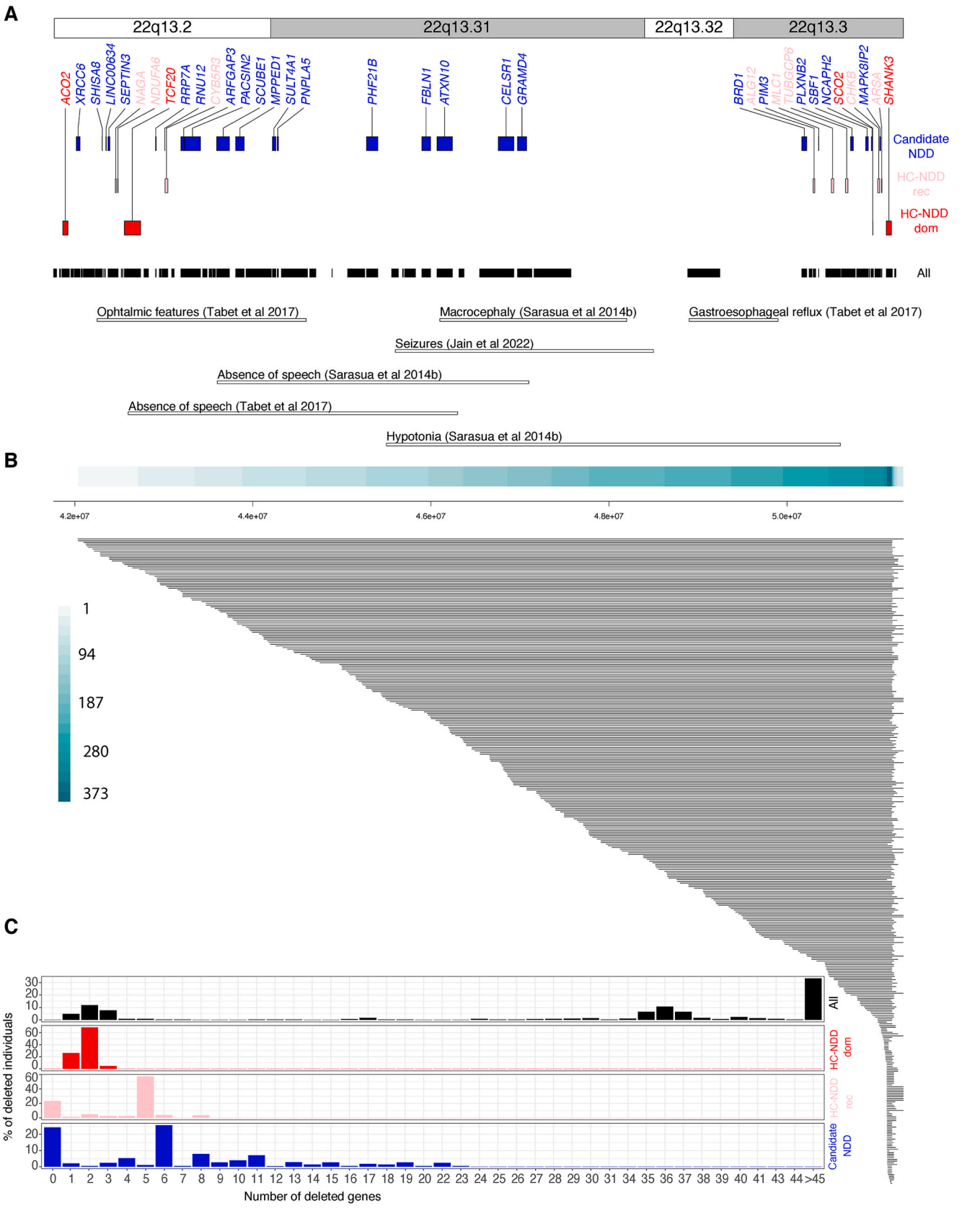
The region of interest was established, using the genomic coordinates of published deletions carried by individuals with PMS (Sarasua et al., 2014a), between the most proximal breakpoint reported so far (hg19; chr22:41,770,054) and the distal part of the chromosome 22 (hg19; chr22:51,304,566). The region contains four cytogenetic subregions of the 22q13 region (22q13.2, 22q13.31, 22q13.32, and 22q13.33) and 110 protein-coding genes, as shown in Fig. 1A. In addition, there are 175 genes encoding non-protein coding RNA within this region.

In order to have a comprehensive view of the deletion size diversity of the 22q13 region in PMS, we integrated the genetic data of 57 individuals with PMS from our French study with the data of 325 patients registered in the PMSF DataHub which has been initiated thanks to the PMS Foundation (https://pmsf.org/). Genetic data were downloaded from the PMSF registry in August 2022 and phenotypic data corresponding to patients included in this study are also available upon request to the PMSF. Interstitial deletions reported in 19 individuals with PMS from literature and two individuals with PMS from our French study are presented separately (Supplemental Fig. 1). As illustrated in Fig. 1B, the breakpoint positions of deletions are dispersed uniformly along the distal part of chromosome 22, resulting in a continuous range of deletion sizes. However, we identified three major groups of individuals with PMS carrying a 22q13 deletion, with distinct numbers of deleted genes: one group of individuals with less than four deleted genes representing 24% of the patients, one group with 35–37 deleted genes representing 24% of the patients and one group with more than 45 deleted genes representing more than 30% of the individuals with PMS (Fig. 1C). A genomic region (chr22:44,850,001-45,630,709 in hg19) appears frequently deleted in individuals with PMS carrying interstitial deletions and contains seven genes (Supplemental Fig. 1).

In the following sections, we describe specific genes located within the 22q13 region that could contribute to the neurological symptoms of individuals with PMS. For this purpose, we used GeneTrek (https://genetrek.pasteur.fr/, Leblond et al., 2021), which gathers different databases related to NDD. Genes are listed in three non-overlapping categories depending on their association level with NDD. The high confidence NDD (HC-NDD) genes correspond to 1,724 genes, which are considered as robustly associated with NDD by at least one of five major sources: SPARK gene list (https://sparkforautism.org/), SFARI (https://www.sfari.org/), SysNDD (https://sysndd.dbmr.unibe.ch/), DDG2P (https://www.deciphergenomics.org/ddd/ddgenes) and DBD (https://dbd.geisingeradmi.org/). The second category includes 5,727 candidate NDD genes, which contain genes with a lower level of confidence for their involvement in NDD (2,143), genes associated with epilepsy, microcephaly or macrocephaly not included in the HC-NDD list, and genes specifically expressed in the foetal and/or adult human brain and/or intolerant to loss of function (LoF) genetic variants. Finally, 12,381 genes are neither HC-NDD nor candidate NDD genes. More details concerning the inclusion criteria for the HC-NDD and the candidate NDD gene lists are provided in Supplemental Figs. 2 and 3. Other information is present on GeneTrek, including the association with epilepsy and micro/macrocephaly. Intolerance to LoF mutations is based on pLI (probability of being LoF intolerant) and LOEUF (LoF observed/expected upper bound fraction). Both metrics were extracted from gnomAD. The LOEUF is a recent metric that considers the length of the gene and the number of samples. It allows estimating the tolerance to LoF mutations with more continuous values than the pLI. A gene with a LOEUF$<$0.35 is considered intolerant to LoF (Karczewski et al., 2020). For brain expression analyses, we used data from BrainSpan and Gtex (https://www.brainspan.org, https://www.gtexportal.org/home/).

Table 1
Frequency of PMS clinical features and chromosome 22q13 associated genomic positions.

Clinical features	Frequency	Genomic region associated (hg 19)	Relative risk (prevalence in carriers of deletions in the associated region)	Reference
Neonatal hypotonia	80% (n = 60)	[45.5 Mb–50.6 Mb]	increased risk	Sarasua et al. (2014a)
Absence of speech	49% (n = 73)	[42.6 Mb–46.3 Mb]	increased risk (80%)	Tabet et al. (2017)
	69% (n = 35)	[43.6 Mb–47.1 Mb]	increased risk	Sarasua et al. (2014a)
Seizures	48% (n = 46)	[45.6 Mb–48.5 Mb]	increased risk	Jain et al. (2022)
Macrocephaly	23% (n = 47)	[46.1 Mb–48.2 Mb]	increased risk	Sarasua et al. (2014a)
Ophthalmic feature	30% (n = 72)	[42.25 Mb–44.6 Mb]	increased risk (70%)	Tabet et al. (2017)
Gastrointestinal reflux	19% (n = 72)	[48.9 Mb–49.9 Mb]	increased risk (70%)	Tabet et al. (2017)



(caption on next page)

Fig. 1. HC-NDD and candidate NDD genes encompassing the regions deleted in patients with PMS. A. Representation of the 22q13 region with all deleted genes displayed in black (n = 110). HC-NDD are genes listed in SFARI I, SPARK, primary SysNDD, DDG2P Brain, or Cognition with a confirmed status and the Tier1 or autosomal recessive inheritance list on Developmental Brain Disorder (DBD). Candidate NDD genes are (i) genes with a lower level of confidence for their involvement in NDD, (ii) genes associated with epilepsy, microcephaly, or macrocephaly, not in the HC-NDD list, and genes specifically expressed in the foetal and/or adult human brain and/or intolerant to LoF genetic variants. HC-NDD genes with a dominant or recessive inheritance are displayed respectively in red (n = 4) and pink (n = 8). Candidate NDD genes are represented in blue (n = 23). Regions associated with ophthalmic features, macrocephaly, seizures, absence of speech, gastroesophageal reflux and hypotonia are also illustrated. **B.** Terminal deletions of patients included in this study are shown by horizontal lines. For patients of the PMSF DataHub (n = 325), genomic coordinates were determined through array technologies and were given either in hg17, hg18, hg19, or hg38. Minimum genomic coordinates were all converted in hg19 using the liftOver package of R (version 1.20.0). Only patients with array data and both start and end genomic coordinates available are shown. We excluded duplicated individuals from France and individuals with multiple events in the region. For patients of our cohort (n = 57), genomic coordinates were validated by CRAM visualisation obtained after whole genome sequencing. A scale representing the number of individuals deleted for the region is shown at the top of the figure. **C.** Distribution of individuals with a 22q13 deletion in function to the number of deleted genes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. The 22q13 region and the HC-NDD and candidate NDD genes

Among 110 protein-coding genes in the 22q13 region, 12 (10.9%) are HC-NDD genes, including four with a dominant inheritance: *ACO2*, *SCO2*, *TCF20,* and *SHANK3*. A total of 21 candidate NDD genes could also participate in the PMS phenotype and account for 19% of the protein-coding genes encompassing the 22q13 region. *RNU12* and *LINC00634,* two genes encoding non-protein-coding RNA, also belong to this category. More than half of individuals with PMS carry deletions encompassing two HC-NDD genes with dominant inheritance (*SHANK3* and *SCO2*) and five HC-NDD genes with recessive inheritance (*ARSA*, *CHKB*, *TUBGCP6*, *MLC1,* and *ALG12*; Fig. 1C).

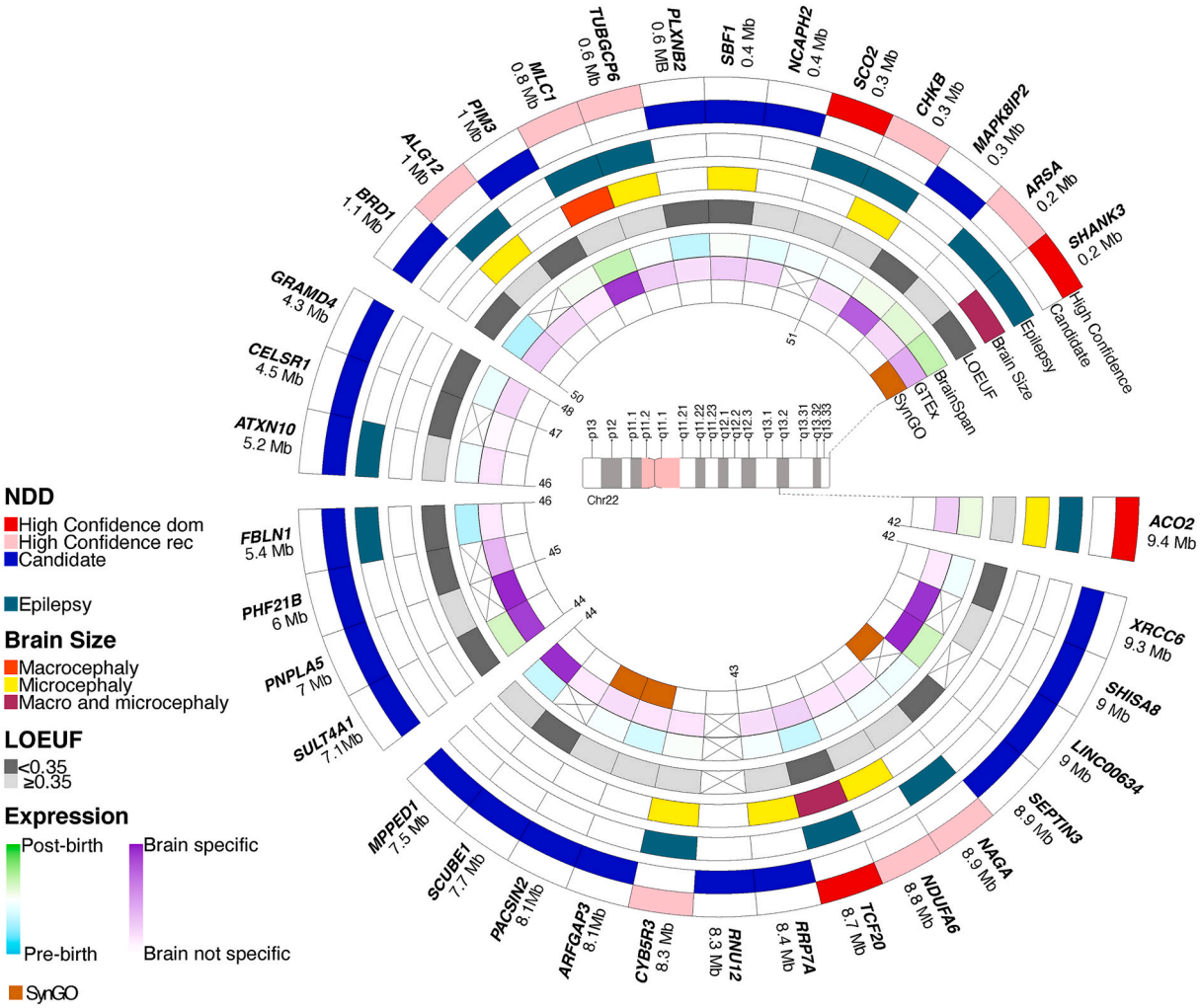


Fig. 2. Characterisation of HC-NDD and candidate NDD genes in the 22q13 region. Each HC-NDD dominant (red) or recessive (pink) and candidate NDD (blue) genes are represented on the circle heatmap. Genes for epilepsy (dark green), microcephaly (yellow), macrocephaly (orange), or both micro/macrocephaly (brown) are taken from HPO (https://hpo.jax.org/app/). Information on tolerance to LoF mutations is displayed in grey in the LOEUF section, with light grey, and dark grey respectively, representing genes tolerant (LOEUF≥0.35) or intolerant (LOEUF<0.35) to LoF mutations. The last section shows 1) a score indicating which genes are more expressed in the pre-birth period (cyan) or the post-birth period (green), 2) a score measuring the brain specificity (purple), and 3) the genes listed in SynGO (light brown). Scores to evaluate brain specificity and temporal expression were calculated using Tau, a metric widely used to evaluate tissue specificity of a gene (Kryuchkova-Mostacci and Robinson-Rechavi, 2016). The plot was constructed with the R package (version 0.4.15) circlize (Gu et al., 2014). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In total, 15 genes of the 35 HC-NDD or candidate NDD genes located in the 22q13 region are predicted to be intolerant to LoF mutations (LOEUF <0.35; Fig. 2). Six HC-NDD or candidate NDD genes (*MLC1*, *PNPLA5*, *SULT4A1*, *MPPED1*, LINC00634, and *SHISA8*) appear to be specifically expressed in the brain (Fig. 2). Several genes are also more expressed during the pre-birth period (e.g., *PLXNB2*, *BRD1*, *FBLN1*, *MPPED1*), while others are more expressed during the post-birth period (e.g., *SHANK3*, *MLC1*, *SULT4A1*; Fig. 2).

Below is a description of the four HC-NDD genes with a dominant inheritance at 22q13.

SHANK3 is deleted or carries point mutations in all individuals with PMS presented here. In the PMS registry, *SHANK3* point mutations represent 12% of individuals with available genetic data. *SHANK3* has been identified as a major gene associated with autism in up to 2% of autistic individuals with ID (Durand et al., 2007; Leblond et al., 2014). *SHANK3* encodes a scaffolding protein that makes the bridge between the actin cytoskeleton and the proteins at the membrane at glutamatergic postsynapses (Boeckers et al., 2002). Many *Shank3* mouse models deleting all or specific isoforms have been generated to study the difference in the cellular phenotype, brain circuit, and neuronal activity compared to wild-type mice. Shank3 deficient mice are characterised by motor dysfunction, reduced cognitive functions, impaired synaptic transmission and plasticity, and abnormal dendritic spine morphology and density (Delling and Boeckers, 2021). Mutations in *SHANK3* were also observed in other psychiatric disorders, such as bipolar disorders and schizophrenia (Gauthier et al., 2010; de Sena Cortabitarte et al., 2017).

SCO2 is deleted in 74% of individuals with PMS and codes for a protein located at the inner membrane of the mitochondria, where it plays a significant role in energy production. *SCO2* encodes a nuclear subunit of the cytochrome *c* oxidase (COX), also known as the complex IV of the mitochondrial chain that is involved in aerobic ATP production. Autosomal recessive mutations in proteins forming this complex represent about 15% of cases of Leigh syndrome, a severe neurological disorder characterised by a loss of psychomotor skills (Lake et al., 2016; Bakare et al., 2021). Other studies highlighted an association of *SCO2* dominant mutations with severe forms of myopia in which the dioptric power is greater than six (Tran-Viet et al., 2013; Wakazono et al., 2016). Mutations leading to this ophthalmic dysfunction are either LoF or missense variant (Tran-Viet et al., 2013; Wakazono et al., 2016). Homozygous and compound heterozygous mutations in *SCO2* have also been reported in individuals with fatal infantile cardioencephalomyopathy (Tay et al., 2004).

TCF20 is deleted in 5% of individuals with PMS and codes for a nuclear protein, acting as a transcriptional coactivator. It regulates the expression of other transcription factors and MMP3, an enzyme implicated in extracellular matrix protein degradation. *TCF20* is associated with a developmental delay with variable intellectual impairment and autism (Lévy et al., 2022). Three *de novo TCF20* mutations were identified in autistic individuals, and an inversion impacting *TCF20* was reported in two brothers with autism and mild ID (Babbs et al., 2014). In line with these results, mice carrying a deletion of *Tcf20* show alteration of the cortical neurogenesis during embryogenesis in addition to impairments in social communication and interaction co-occurring with excessive repetitive behaviour (Feng et al., 2020).

The mitochondrial aconitase enzyme encoded by ***ACO2*** is deleted in very few patients who carry very large 22q13 deletions (>9 Mb). It catalyses the second reaction of the Krebs cycle consisting of the isomerisation of citrate to isocitrate. Homozygous or compound heterozygous variants in *ACO2* lead to infantile cerebellar retinal degeneration, a rare recessive neurodegenerative disorder (ICRD; Spiegel et al., 2012; Sharkia et al., 2019). Patients with ICRD present development delay, ophthalmological defects, atrophy of the cerebellum, epilepsy, and microcephaly (Spiegel et al., 2012; Sharkia et al., 2019). The severity of ophthalmological impairments correlates with a deficit in aconitase activity (Metodiev et al., 2014; Sharkia et al., 2019). A large proportion of patients are also nonverbal and nonambulatory. When isolated, optic neuropathies can be due either to dominant or recessive *ACO2* mutations (Guehlouz et al., 2021). Other disorders are related to mutations in *ACO2,* such as hereditary spastic paraplegia and optic atrophy 9 (Marelli et al., 2018; Tozawa et al., 2021). In the case of optic atrophy, there is both dominant and recessive inheritance (Charif et al., 2021).

Besides the four dominant HC-NDD genes presented above, 8 HC-NDD recessive genes and 23 candidate NDD genes might also be involved in various disorders affecting the brain or other organs and could contribute to many clinical features of individuals with PMS, as shown in Table 2. Since epilepsy, microcephaly, and macrocephaly are neurological-related symptoms reported in PMS, we used the human phenotype ontology (HPO) terms to select genes located in the 22q13 region associated with these phenotypes. More details about their biological function and involvement in epilepsy, microcephaly, and macrocephaly are presented below.

4. The 22q13 region and epilepsy

Epilepsy is a common comorbidity in individuals with PMS, with a frequency that fluctuates between 17% and 70% and a lifelong increase (Holder et Quach, 2016, De Coo et al., this issue; Schön et al., this issue). The type of epilepsy in PMS patients varies between febrile, focal, atonic, tonic-clonic, tonic, and myoclonic seizures (Jain et al., 2022). The seizure frequency and trigger are also variable among patients (Jain et al., 2022). Why some individuals with PMS develop epilepsy and others do not remains unclear. Contrary to other comorbidities, such as the absence of speech, a number of studies failed to find a strong correlation between epilepsy prevalence and deletion sizes (Reierson et al., 2017; Sarasua et al., 2014b; Tabet et al., 2017). However, one study found an increasing proportion of patients with PMS and epilepsy carrying large deletions >4 Mb (Jain et al., 2022). Interestingly, the parental origin of the affected chromosome has been suggested to play a role in seizure development, with a higher risk for deletion occurring on the maternal chromosome (Sarasua et al., 2014b). Better knowledge of the genetic factors involved in epilepsy is important for treating the seizures occurring in individuals with PMS (Musto et al., 2020).

Based on HPO terms, we established a list of 1,736 candidate genes for epilepsy. In total, 13 of them (*SHANK3, ARSA, CHKB, SCO2, TUBGCP6, MLC1, ALG12, ATXN10, FBLN1, CYB5R3, TCF20, NAGA* and *ACO2*) map to the 22q13 region (Fig. 2).

Manifestations of at least one epileptic event during a lifetime have been reported in two patients with a frameshift mutation affecting ***SHANK3*** (Holder and Quach, 2016). Both patients were 14 years old and were affected by atypical absence epilepsy. The first seizures of patient 1 appeared at 7 years of age and occurred multiple times per week with a duration of 3–5 min. Onset of epilepsy was at 14 years of age for patient 2, and seizures spanned 3 min. In another study, among 15 autistic individuals carrying a genetic variant in *SHANK3*, 6 presented with epilepsy (Leblond et al., 2014). Similarly, 29% of a cohort with 17 carriers of a LoF mutation in *SHANK3* also developed epilepsy (De Rubeis et al., 2018). Despite the large number of mutant mice for *Shank3*, epilepsy has been barely observed in this model (Peça et al., 2011). In contrast, mice overexpressing *Shank3* display spontaneous seizures, as shown in two different studies (Han et al., 2013; Jin et al., 2018).

ARSA (deleted in 77% of PMS individuals) encodes an enzyme expressed in lysosomes implicated in the degradation of sulfatide, a lipid located in the nervous system's myelin. Low activity of ARSA leads to metachromatic leukodystrophy (MLD), a rare neurodegenerative disorder characterised by progressive motor and cognitive impairments. This disorder is mainly caused by autosomal recessive mutations in *ARSA*. Depending on the level of ARSA activity, the onset of MLD varies between adult (15–20% of cases), juvenile (20–30% of cases), and late infantile (50–60% of cases), which is the most common and severe form (Shaimardanova et al., 2020). Epilepsy has been reported in two

Table 2
Genes in the 22q13 regions and their associated diseases. Genes and associated diseases were extracted from the OMIM morbid map. OMIM ID is given for each phenotype. HC-NDD genes with a dominant or recessive inheritance are displayed respectively in red and pink. Candidate NDD genes and other genes are displayed respectively in blue and black.

Gene	morbid MAP, OMIM id
From 40 Mb to 42 Mb	
AC02	Infantile cerebellar-retinal degeneration, 614559
	Orofacial cleft 10, 613705
From 42 Mb to 44 Mb	
MEI1	Hydatidiform mole, recurrent, 3, 618431
CCDC134	Osteogenesis imperfecta, type XXII, 619795
TNFRSF13C	Immunodeficiency, common variable, 4, 613494
NAGA	Kanzaki disease, 609242
	Schindler disease, type I and III, 609241
	Schindler disease, type III, 609241
NDUFA6	Mitochondrial complex I deficiency, nuclear type 33, 618253
CYP2D6	Codeine sensitivity, 608902
	Debrisoquine sensitivity, 608902
TCF20	Developmental delay with variable intellectual impairment and behavioural abnormalities, 618430
RRP7A	Microcephaly 28, primary, autosomal recessive, 619453
CYB5R3	Methemoglobinemia, type I, 250800
	Methemoglobinemia, type II, 250800
A4GALT	NOR polyagglutination syndrome, 111400
	Blood group, P1Pk system, P(2) phenotype, 111400
	Blood group, P1Pk system, p phenotype, 111400
From 44 Mb to 46 Mb	
FBLN1	Synpolydactyly, 3/3'4, associated with metacarpal and metatarsal synostoses, 608180
From 46 Mb to 48 Mb	
ATXN10	Spinocerebellar ataxia 10, 603516
PPARA	Hyperapobetalipoproteinemia, susceptibility to
TRMU	Liver failure, transient infantile, 613070
	Deafness, mitochondrial, modifier of, 580000
CELSR1	Lymphatic malformation 9, 619319
From 48 Mb to 50 Mb	
From 50 Mb to 52 Mb	
ALG12	Congenital disorder of glycosylation, type Ig, 607143
MLC1	Megalencephalic leukoencephalopathy with subcortical cysts, 604004
MOV10L1	Spermatogenic failure 73, 619878
TUBGCP6	Microcephaly and chorioretinopathy, autosomal recessive, 1, 251270
SBF1	Charcot-Marie-Tooth disease, type 4B3, 615284
SCO2	Mitochondrial complex IV deficiency, nuclear type 2, 604377
	Myopia 6, 608908
TYMP	Mitochondrial DNA depletion syndrome 1 (MNGIE type), 603041
CHKB	Muscular dystrophy, congenital, megaconial type, 602541
ARSA	Metachromatic leukodystrophy, 250100
SHANK3	Phelan-McDermid syndrome, 606232
	Schizophrenia 15, 613950
ACR	Male infertility due to acrosin deficiency

independent cases of patients with juvenile MLD and recessive variants in *ARSA* (Kang et al., 2010; Barboura et al., 2022).

CHKB (deleted in 75% of PMS individuals) is involved in the metabolism of phospholipids and is the causative gene of congenital muscular dystrophy. Clinical features of 15 patients carrying *CHKB* mutations between 38 days of age and 17 years of age were analysed. Among them, three individuals carrying recessive variants in *CHKB* were subject to a single epilepsy history (Haliloglu et al., 2015).

Epilepsy has also been observed in three children with hypertrophic cardiomyopathy and COX deficiency (Jaksch et al., 2000). They belong to two unrelated families where pathogenic mutations in ***SCO2*** segregate. The three patients carried compound heterozygous genetic variants and shared one predicted deleterious missense variant E140K (Jaksch et al., 2000).

Epilepsy is a frequent comorbid phenotype of megalencephalic leukoencephalopathy with subcortical cysts (MLC), which is observed in 75% of cases with ***MLC1*** homozygous recessive mutations. This gene (deleted in 68% of PMS individuals) codes for a protein specifically expressed in astrocytes (Leegwater et al., 2001; Yalçinkaya et al., 2003). Epilepsy severity varies, ranging from mild to severe cases with status epilepticus. In general, antiepileptic treatments efficiently control mild epilepsy in MLC patients (van der Knaap et al., 2012). In addition, *Mlc1* deficient mice exhibit signs of higher epilepsy susceptibility, including hindlimb clasping, abnormal electrical activity, and lower seizure threshold. Induced epilepsy is also more severe in these mice than in wild-type littermates (Dubey et al., 2018).

ALG12 (deleted in 65% of PMS individuals) is one of the causative genes of a multi-system disorder called congenital disorder of glycosylation (CGC) type Ig. The encoded protein is a reticulum enzyme with transferase activity essential for protein glycosylation. Other types of CGC exist and imply different genes with gene-specific phenotypes (Haeuptle and Hennet, 2009). Concerning ALG12-CGC, the disorder is inherited with a recessive model, and some patients affected by this disorder also display epilepsy (Tahata et al., 2019).

Generalised motor epilepsy is recurrently observed in spinocerebellar ataxia type 10, whose origin is due to the expansion of a 5 nucleotides pattern (ATCCT) located in intron 9 of ***ATXN10*** (deleted in 30% of PMS individuals; Rasmussen et al., 2001). There is an increased risk of developing epilepsy when ACTTC repeats are interrupted by a heptanucleotide pattern (ATTTTCT or ATATTCT) or when a first-degree relative also has epilepsy (McFarland et al., 2014). However, in the case of PMS, the 22q13 deletion leads to a loss of one copy of *ATXN10,* and there is no report of epilepsy in patients with *ATXN10* haploinsufficiency.

CYB5R3 (deleted in 8% of PMS individuals) codes for two isoenzymes. Isoform 1 is a soluble protein expressed specifically in erythrocytes, whereas isoform 2 is expressed in all tissues and binds to the outer mitochondrial membrane, the endoplasmic reticulum, and the plasma membrane. Mutations in *CYB5R3* cause a rare disease called recessive hereditary methemoglobinemia (RHM) which exists in two forms: RHM type I and RHM type II. RHM type II is the most severe form, with a deficiency in the membrane-anchored isoform, which is essential for various metabolic transformations. RHM type II results in diverse neurological impairments, including epilepsy in 16% of the patients, the majority being pharmaco-resistant (Nicita et al., 2022).

The presence of epilepsy in carriers of variants in ***TCF20*** has been evaluated in four studies (Lelieveld et al., 2016; Schäfgen et al., 2016; Torti et al., 2019; Vetrini et al., 2019). Altogether, 64 individuals were reported, and 12 (19%) exhibit diverse forms of seizures, including focal epilepsy, febrile seizure, nocturnal epilepsy, and epilepsy with multifocal origin. Among those individuals, 11 were heterozygous for a LoF variant, and one was heterozygous for an H1909Y missense variant.

NAGA (deleted in 4% of PMS individuals) encodes a lysosomal enzyme involved in the catabolism of glycoproteins, sphingolipids, and oligosaccharides. Deficiency in *NAGA* results in one of the three types of Schindler disease, a rare and recessive lysosomal storage disorder characterised by central and peripheral axonopathy associated with rapid psychomotor degradation. This disorder was discovered in two siblings presenting early onset neurodegeneration, seizure disorders, and hypotonia (Desnick and Wang, 1990).

In the case of infantile cerebellar retinal degeneration (ICRD) due to mutations in ***ACO2***, the analysis of clinical features of eight individuals from two unrelated and consanguineous families showed that six of them developed generalised or focal epilepsy (Spiegel et al., 2012). All carriers were heterozygous for an S112R missense variant. Recently, a database gathering extensive clinical information on 123 individuals with *ACO2* dominant or recessive mutations was developed (https://www.lovd.nl/ACO2). Among 21 patients affected by a recessive neurodegenerative syndrome, 13 (62%) also suffered from seizures (Guehlouz et al., 2021).

While they are listed in the HPO for epilepsy, there is, to our knowledge, no report of epilepsy in carriers of variants affecting *FBLN1* and *TUBGC6P* in the literature.

5. The 22q13 region and macro/microcephaly

Microcephaly and macrocephaly are neurological conditions characterised by abnormal cranial circumference. In the case of macrocephaly, the head size, measured around the forehead and the occipital protuberance, is above two standard deviations (SD) or more for a given age, ethnicity, and sex (respectively below two SD or more for microcephaly, although in some studies it could be defined below three SD). Interestingly, both of these conditions are reported in patients with PMS (17% with macrocephaly and 16% with microcephaly).

Along the 22q13 region, eight genes are associated with microcephaly according to the annotated HPO terms: *CHKB*, *SBF1*, *TUBGCP6*, *ALG12*, *CYB5R3*, *RRP7A*, *NDUFA6*, *ACO2*; only one gene is associated with macrocephaly: *MLC1*; and two genes to both: *SHANK3* and *TCF20* (Fig. 2).

In a study providing deep phenotyping of 14 individuals with a point mutation in ***SHANK3***, one patient displayed microcephaly, and one displayed macrocephaly (De Rubeis et al., 2018). Furthermore, a meta-analysis focused on *SHANK* genes reported an additional case carrying a *de novo* frameshift mutation in *SHANK3* and exhibiting microcephaly (Leblond et al., 2014).

Likewise, different studies have described microcephaly in carriers of homozygous recessive ***CHKB*** mutations (Mitsuhashi et al., 2011; Haliloglu et al., 2015). Cranial MRI of these microcephalic individuals showed no structural brain abnormalities (Mitsuhashi et al., 2011).

SBF1 (deleted in 73% of PMS individuals) is a gene coding for an inactive phosphatase and is included in the myotubularin family. *SBF1* is associated with the CMT4B3 subtype of Charcot-Marie-Tooth disease, a disorder of the peripheral nervous system (Nakhro et al., 2013; Gang et al., 2020). This specific subtype is characterised by autosomal recessive inheritance and impacts both the sensory/motor axons and the myelin. Early onset microcephaly often co-occurs with the neuropathy caused by recessive *SBF1* mutations, as observed in siblings of four different families (Flusser et al., 2018).

TUBGCP6 (deleted in 70% of PMS individuals) is a member of the g-tubulin ring complex family. The encoded protein plays a major role in microtubule nucleation at the centrosome and is, therefore, essential for cell division and cell migration. Interestingly, recessive mutations in *TUBGCP6* have been recurrently detected in patients with microcephaly associated with retinopathy (Puffenberger et al., 2012; Martin et al., 2014; Hull et al., 2019; Shurygina et al., 2020).

Concerning ***MLC1***, patients with MLC disease are characterised by progressive macrocephaly (Yalçinkaya et al., 2003; van der Knaap et al., 2012). This phenotype develops during the very early infancy of patients, generally within the first four weeks before a stabilisation of the head growth (van der Knaap et al., 2012).

In the case of ***ALG12***, patients with CGC-ALG12 carrying compound heterozygous or homozygous variants often present progressive

microcephaly (Tahata et al., 2019; Hiraide et al., 2021; Nicotera et al., 2021).

Microcephaly has also been observed in a case with RHM2 carrying two heterozygous mutations in ***CYB5R3*** (Mannino et al., 2018). In addition, among 50 patients with RHM2 due to recessive variants in *CYB5R3*, more than half displayed microcephaly (Nicita et al., 2022).

RRP7A (deleted in 6% of PMS individuals) codes for a protein expressed in radial glial cells and ependymal cilia during brain development. Recently, a deleterious *RRP7A* homozygous missense variant in *RRP7A* was identified in eight members of a consanguineous family with severe microcephaly (Farooq et al., 2020). Zebrafish homozygous for a frameshift mutation in *RRP7A* also display smaller brain sizes than wild-type fish (Farooq et al., 2020). Reduction in brain size may result from a defect in rRNA processing and impaired primary cilia resorption leading to alteration of cell proliferation in the course of neurogenesis (Farooq et al., 2020).

Patients with ***TCF20*** mutations can exhibit either microcephaly or macrocephaly. For macrocephaly, 13 cases heterozygous for *TCF20* LoF variants have been published (Torti et al., 2019; Vetrini et al., 2019). Microcephaly is less reported in patients with *TCF20* mutations. However, a reduction in brain size is observed in homozygous *Tcf20* knockout mice (Feng et al., 2020).

NDUFA6 (deleted in 4% of PMS individuals) codes for a nuclear subunit of NADH dehydrogenase, representing the first electron entry in the respiratory chain. Clinical evaluation of one carrier of a homozygous pathogenic mutation in *NUDFA6* shows a reduction of head growth noticed at 5 years old (Alston et al., 2018).

Finally, a cohort of 16 patients homozygous or compound heterozygous for ***ACO2*** mutations showed that 75% of them were diagnosed with severe microcephaly. Head growth defects in these patients occurred between the first and third years of age (Sharkia et al., 2019).

6. The 22q13 region and synaptic genes

Synapses play major roles in information processing, and their dysfunction can lead to brain disorders such as neurodevelopmental and psychiatric disorders (Bourgeron, 2009; Lepeta et al., 2016). A large number of synaptic proteins participate in developing and maintaining synapses to ensure their organisation and activities. Cellular localisation and functions of synaptic proteins are well documented in SynGO, a knowledge base initiated by a scientific consortium (https://www.syngoportal.org/). Within the 22q13 region, only four genes are listed in SynGO: *SEPTIN3* and *ARFGAP3* are classified as coding for presynaptic proteins, *SHANK3* codes for a postsynaptic protein, and *PACSIN2* appears as a modulator of the synaptic transmission (Fig. 3).

SHANK3 is enriched at the postsynaptic density of glutamatergic neurons. Composed of five domains, SHANK3 acts as a master scaffolder by interacting with multiple other synaptic proteins. Partners of SHANK3 comprise glutamatergic metabotropic, NMDA and AMPA receptors, signalling proteins, other intermediate scaffolding proteins, and cytoskeleton proteins (Sheng and Kim, 2000). The role of SHANK3 is to maintain the protein architecture of the synapse. In addition, it participates in receptor signalling and thus is essential for synaptic transmission, plasticity, and homeostasis (Verpelli et al., 2011; Tatavarty et al., 2020). During brain development, SHANK3 is also involved in forming dendritic spines (Durand et al., 2012; Gouder et al., 2019; Peça et al., 2011).

PACSIN2 (deleted in 10% of PMS individuals) belongs to a protein kinase family important for endocytosis processes (Kessels and Qualmann, 2004). These proteins interact with multiple molecules implicated in different steps of endocytosis, including N-WASP, which activate the Arp2/3 complex and dynamin, with both acting in the plasma membrane fission for vesicle release in the cytosol (Kessels and Qualmann, 2004). PACSIN proteins also recycle AMPA receptors at the plasma membrane required for long-term depression induction, which is a cellular mechanism underlying plasticity, learning, and memory. AMPA receptor trafficking at the postsynaptic membrane is induced by the binding of PACSIN1 and PACSIN2 to proteins involved in the endocytosis of AMPA receptors, such as PICK1 (Anggono et al., 2013).

ARFGAP3 (deleted in 9% of PMS individuals) proteins are located at the Golgi apparatus in the presynaptic area of neurons. The proteins regulate the retrograde transport of vesicles from the Golgi to the endoplasmic reticulum and within the intra-Golgi cisternae (Spang et al., 2010). ARFGAP3 participates in the COPI coat assembly, a coat protein complex that initiates the budding process on the cis-Golgi membrane. This COPI coat assembly is critical during vesicle formation (Kartberg et al., 2010). ARFGAP3 functions also include the regulation of Arf1 activities and endocytic membrane traffic in retinal photoreceptor synapses (Dembla et al., 2014).

SEPTIN3 (deleted in 3% of PMS individuals) is a member of the large GTPase protein family and is predominantly expressed at the presynaptic nerve terminal of mature neurons across many different brain regions (Xue et al., 2004; Peterson et al., 2007). Septin proteins associate with each other to form hetero-octamer or hetero-hexamer structures.

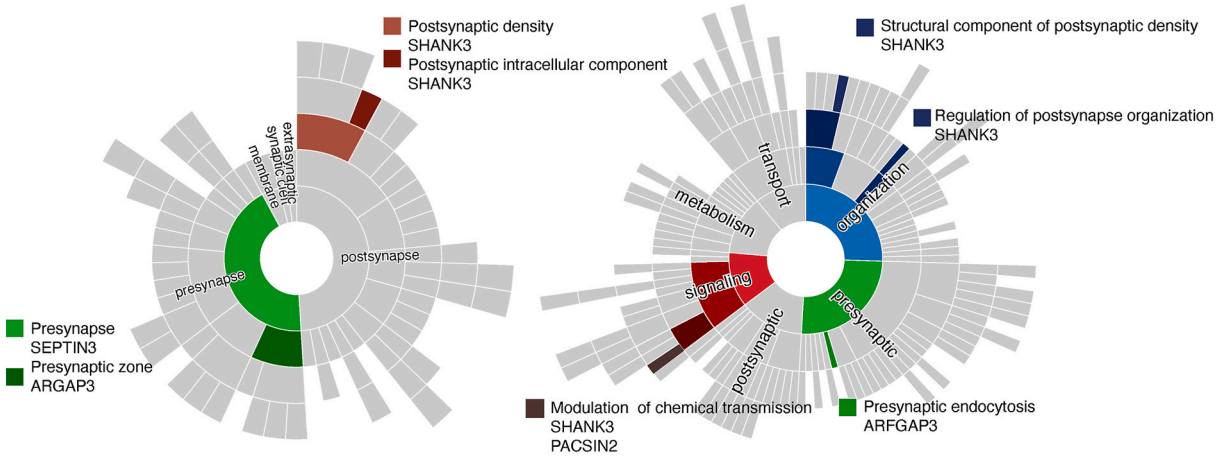


Fig. 3. Synaptic locations and functions of genes of the 22q13 region. SynGO sunburst plot of the four synaptic genes in the 22q13 region (https://www.syngoportal.org/). The first plot shows the compartmental synaptic location, and the second shows the genes' biological function. The inner layers provide general information, and the outer layer provides more specific detail. Sections are coloured if a gene of the query list belongs to the category. Grey sections correspond to categories with no genes in the query list. The 22q13 region contains two genes coding for presynaptic proteins (SEPTIN3; ARFGAP3) and one gene coding for a postsynaptic protein (SHANK3). Biological functions include modulation of chemical synaptic transmission (SHANK3; PACSIN2), structural constituent of postsynaptic density (SHANK3), and presynaptic endocytosis (ARFGAP3).

One such complex comprises SEPTIN2, SEPTIN3, SEPTIN6, and SEPTIN7, with SEPTIN3 placed at the centre of the resulting filament (DeRose et al., 2020). Septin proteins are involved in diverse functions, including exocytosis, neural cell migration, neuritogenesis, and spinogenesis (Tokhtaeva et al., 2015; Ageta-Ishihara and Kinoshita, 2021). However, due to possible redundant functions of these proteins, it is still challenging to delineate the precise role of SEPTIN3 in the brain.

7. Discussion

The vast majority of the individuals with PMS display global developmental delay, ID, absent or delayed speech, neonatal hypotonia together with minor dysmorphic features (long eyelashes, dolichocephaly, bulbous nose, large fleshy hands, and others). They can also suffer from other non-specific clinical features, including epilepsy, microcephaly, macrocephaly, and sleep disorders, as well as complications related to the kidney, the heart, and the ophthalmic system (Schön et al., this issue). In most cases, PMS co-occurs with psychiatric conditions such as ASD, depressive episodes, anxiety symptoms, and bipolar disorder. In addition, regression, or loss of motor skills, is often observed in adolescence, with possible recovery occurring after a variable period of time (Kohlenberg et al., 2020; Reierson et al., 2017; van Balkom et al., this issue).

In individuals with *SHANK3*-related PMS, there is also a wide variability of the type and the size of the deletion. The distribution of the breakpoint position is mostly uniform along the 22q13 region, with the exception of a recurrent breakpoint within the *SHANK3* gene (Fig. 1B, Bonaglia et al., 2006; Durand et al., 2007). More than half of individuals with PMS carrying a 22q13 deletion are haploinsufficient for at least 34 genes, including seven genes previously associated with NDD (Fig. 1C). Patients with larger deletion are more likely to present macrocephaly, severe developmental delay, or some dysmorphic features (Soorya et al., 2013; Sarasua et al., 2014b). In addition, the absence of speech is more frequent in individuals with a deletion disrupting the genomic region from position 42.6–46.3 Mb (Tabet et al., 2017). Other genomic regions could be associated with gastrointestinal disorders, ophthalmic features, and epilepsy, although there are inconsistent results between studies (Tabet et al., 2017; Jain et al., 2022).

Due to its terminal position on chromosome 22 and its biological functions, *SHANK3* has been considered the primary gene for PMS neurological features. Patients with a point mutation in *SHANK3* share the core symptoms and similar frequency with patients carrying a deletion of the 22q13 region (Schön et al., this issue). However, individuals with *SHANK3*-unrelated PMS have overlapping PMS phenotypes suggesting the contribution of other genes at 22q13 than *SHANK3*. For example, *PHF21B* corresponds to a candidate NDD gene which is deleted in 13 individuals over the 21 individuals carrying an interstitial deletion of variable size not affecting *SHANK3* (Supplemental Fig. 1). *PHF21B* codes for a PHD finger protein specifically expressed in the cortex and is critical for neural stem cell differentiation during brain formation (Basu et al., 2020). The *PHF21B* gene was proposed as a susceptibility gene for major depression in humans (Wong et al., 2017), and mice deleted for *Phf21B* display an impaired social memory in addition to a reduced expression of several synaptic genes (Chin et al., 2022).

We reported information on HC-NDD or candidate NDD genes that could, in addition to *SHANK3* haploinsufficiency, contribute to the large diversity of neurological phenotypes developed by individuals with PMS (Fig. 1). *TCF20*, *SCO2,* and *ACO2* are HC-NDD genes with an autosomal dominant inheritance pattern. Deletions of these genes can therefore have a significant impact on the PMS phenotype. *SCO2* is located in the subterminal part of chromosome 22 and is frequently deleted in patients with PMS (74% of the patients presented here). Haploinsufficiency of *SCO2* may increase the risk of developing myopia, although this phenotype is not often observed in individuals with PMS (Tran-Viet et al., 2013). Other symptoms associated with Leigh syndrome should be considered with precaution, as mutations causing this disorder follow a recessive inheritance pattern. *ACO2* and *TCF20* are only involved in larger deletions (9.4 Mb and 8.7 Mb, respectively) which affect fewer patients (<5% of the patients presented here). In a subset of individuals with PMS with very large deletions, *TCF20* could add to the severity of a large set of clinical features observed, such as ID, language delay, autism, hypotonia, seizures, dysmorphic facial features, macrocephaly, gastrointestinal, and ophthalmologic abnormalities (Torti et al., 2019; Vetrini et al., 2019). The rare patients with a 22q13 deletion disrupting *ACO2* could be more susceptible to developing gradual optical defects during their infancy since ocular function degeneration represents the main phenotype caused by a dominant or recessive mutation in *ACO2* (Charif et al., 2021; Guehlouz et al., 2021).

For a large number of HC-NDD or candidate NDD genes located in the 22q13 region, inheritance follows a recessive model (Fig. 1A). For some patients, the deletion could unmask a heterozygous variant affecting these genes on the non-deleted allele located on the intact chromosome 22 and therefore increasing the risk of developing additional clinical features. This mechanism has been described in other deletion syndromes, such as Smith-Magenis syndrome (DeRose et al., 2020) and the 16p11.2 syndrome (Pebrel-Richard et al., 2014). Such LoF mutations on the intact chromosome 22 might be more frequent than expected since many genes with recessive inheritance are relatively tolerant to LoF mutations (pLI≤ 0.9; LOEUF ≥0.35, Supplemental Fig. 4). *TYMP* and *NDUFA6* are two examples of recessive genes tolerant to LoF variants and critical for mitochondrial functioning (Alston et al., 2018; Bax, 2019). Deleterious mutations in the non-deleted allele of these genes could affect organs with high energy demand, such as the brain, but also the heart, the skeletal muscle, and the kidney, and cause cardiac defects and renal disorders observed in patients with PMS. Another interesting example of such LoF tolerant and recessive gene is *ARSA,* which has been suggested to increase the risk of regression in patients with PMS (De Coo et al., this issue). MLD resulting from the unmasking of a missense variant was observed in a PMS patient presenting with regression (Ahn et al., 2020). While it seems that there are no genes subject to genomic imprinting in the 22q13 region, epigenetic mechanisms might also contribute to the clinical heterogeneity of PMS. Indeed, patients carrying large deletions (>1 Mb) display a distinct DNA methylation pattern compared to control individuals and patients carrying smaller deletions or point mutations in *SHANK3* (Schenkel et al., 2021). This specific methylation pattern is associated with a similar metabolic profile (e.g., reduced utilisation of aerobic energy and abnormal response to metabolic stress). Interestingly, patients with PMS showing these epigenetic and metabolic patterns are all deleted for *BRD1*, a candidate NDD gene encoding a protein interacting with DNA and histone tails.

We found 13 genes listed as epilepsy genes in HPO (Fig. 2), but weak evidence from the literature for *FBLN1* and *TUBGCP6*. While *CELSR1* is not part of the HPO epilepsy list, it could be of particular interest as it is located in the region previously associated with a higher risk of developing epilepsy (Jain et al., 2022). Moreover, a recent study suggested a possible association between epilepsy and variants detected in *CELSR3*, a paralog of *CELSR1* (Li et al., 2022). Interestingly, *ARSA* listed in the epilepsy HPO term is associated with morphologic changes of the white matter that could explain the increased risk of developing seizures in individuals with deficiency for this gene (De Coo et al., this issue).

For abnormal head growth, we presented 10 genes associated with microcephaly and 3 genes associated with macrocephaly (Fig. 2), but other genes not listed in these HPO terms could be considered. For example, a minimal region shared by all individuals with *SHANK3*-unrelated PMS highlighted the possible role of *PARVB* in macrocephaly (Disciglio et al., 2014).

The 22q13 region contains four synaptic genes: *SHANK3*, *ARFGAP3*, *SEPTIN3,* and *PACSIN2* (Fig. 3). They ensure the correct functioning of synapse and synaptic transmission. Alterations of synaptic genes are often associated with neuropsychiatric conditions or NDD. For example,

mutations in *SHANK3* have been reported in multiple neuropsychiatric conditions, including ASD, schizophrenia, and bipolar disorders (Durand et al., 2007; Gauthier et al., 2010; Leblond et al. 2014; de Sena Cortabitarte et al., 2017). *SHANK3* is also strongly associated with ID, which represents a frequent clinical feature of PMS. Higher susceptibility for psychiatric disorders in PMS could also be due to brain-expressed genes such as *MLC1,* which has been associated with catatonic schizophrenia in several studies (Meyer et al., 2001; Verma et al., 2005; Selch et al., 2007). Postsynaptic genes may also include the candidate NDD gene *MAPK8IP2,* which is enriched in the postsynaptic densities in mice (Giza et al., 2010).

We focused this review on genes that could contribute to the neurological phenotypes of individuals with PMS. An overview of genes within the 22q13 region and their possible contribution to other PMS phenotypes, such as gastrointestinal and urinary tract malformations or heart defects, was previously reported (Ricciardello et al., 2021). Additional lists of genes associated with HPO terms described by Schön et al. are available in Supplemental Table 1. Interestingly, most HC-NDD genes are associated with more than 10 HPO terms related to symptoms observed in individuals with PMS.

We also limited this review to the protein-coding genes, but another trail to explore is the role of the non-coding regions, which represent 98% of the genome. Non-coding DNA includes promoter, 3′UTR, 5′UTR, enhancer, silencer, non-coding RNA, and TAD boundaries that regulate gene expression (Turner and Eichler, 2019). The contribution of the non-protein-coding segment of the genome in diseases has been studied in multiple genetic brain disorders (Medico-Salsench et al., 2021). CNVs disrupting non-coding regions located near epilepsy genes were found to be enriched in patients with epilepsy and less frequent in controls (Monlong et al., 2018). Likewise, variants falling in UTR regions, foetal promoters, and embryonic enhancers were significantly enriched in autistic individuals compared to their undiagnosed siblings (Turner et al., 2017). Genome-wide association studies also highlighted the importance of loci associated with a difference in gene expression during the developmental period and allowed the discovery of expression quantitative trait loci (eQTL) that collectively increase the risk of developing neuropsychiatric conditions like bipolar disorder, schizophrenia, and attention deficit with or without hyperactivity (O'Brien et al., 2018). Analysis of eQTL, therefore, represents a promising approach to improve our understanding of phenotypic variability in complex disorders such as PMS.

Finally, the diversity of clinical symptoms may also be modulated by rare or common variants located outside the 22q13 region. Additional CNVs disrupting an NDD gene were identified in 65% of patients with PMS (Tabet et al., 2017). Such multiple hits present in the patient genomes, including CNV, SNV, and indel variants, could increase the phenotypic severity following an additive or a synergic model. In autism, full-scale IQ is lower in individuals accumulating more than one clinically relevant variant in NDD genes (Guo et al., 2019). Likewise, another study highlighted a reduced full-scale IQ in individuals carrying more than two high-impact *de novo* variants affecting LoF intolerant genes (Warrier et al., 2022). Common variants could also modulate the severity of the symptoms. For example, the polygenic score for schizophrenia is higher in carriers of 22q11.2 deletion diagnosed with schizophrenia (Davies et al., 2020). In contrast, additional variants could have a protective effect on some clinical features. More research on these additive risk or resilience factors is highly needed.

In summary, this review of the genes at chromosome 22q13 indicates that several genes might influence the complex and heterogeneous clinical trajectories of individuals with PMS. Loss of a single copy of *SHANK3* recapitulates many of the symptoms of PMS, but further studies should consider the surrounding genes at chromosome 22q13, other genetic variations on the remaining non-deleted allele, and more widely in the genome that might modulate the severity of the symptoms. This has importance for appropriate caregiving and clinical trials. Understanding the genotype-phenotype relationship in PMS will require very large-scale genetic and phenotypic data across countries and the possibility of securely sharing the data with the scientific/medical community and family associations.

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest related to the publication of this study.

CRediT authorship contribution statement

Aline Vitrac: Writing – original draft, Investigation, Formal analysis, Visualization. **Claire S. Leblond:** Methodology, Formal analysis, Writing – review & editing. **Thomas Rolland:** Methodology, Formal analysis, Writing – review & editing. **Freddy Cliquet:** Methodology, Formal analysis. **Alexandre Mathieu:** Data curation. **Anna Maruani:** Investigation, Resources. **Richard Delorme:** Investigation, Resources. **Michael Schön:** Writing – review & editing. **Andreas M. Grabrucker:** Conceptualization, Writing – review & editing. **Conny van Ravenswaaij-Arts:** Writing – review & editing. **Katy Phelan:** Writing – review & editing. **Anne-Claude Tabet:** Investigation, Resources. **Thomas Bourgeron:** Conceptualization, Writing – original draft, Supervision.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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